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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,324	06/22/2001	Juha Punnonen	0169.310US	7238

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EXAMINER	
OUSPENSKI, ILIA I	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,324	PUNNONEN ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004 and 26 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *259-381* is/are pending in the application.

4a) Of the above claim(s) *302 – 367 and 369 - 381* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *259 – 301 and 368* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 07/28/2004, is acknowledged.

However, the amendment fails to place the instant application in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequence disclosed at least in claim 291 *is not accompanied by SEQ ID Numbers*. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification and the claims accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

2. Applicant's election without traverse of Group I, claims 259 – 301 and 368, drawn to polypeptides, in the reply filed on 03/26/04 is acknowledged.

Claims 1 – 258 have been cancelled.

Claims 259 – 381 are pending.

Claims 302 – 367 and 369 - 381 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 259 – 301 and 368 are under consideration in the instant application.

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The provisional applications 60/213,946 and 60/241,245 upon which priority is claimed appear to provide adequate support under 35 U.S.C. 112 for claims of this application.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the elected claims are directed.*

In addition, Applicant should avoid the use of the word "novel" in the title, as patents are presumed to be novel and unobvious.

5. Applicant's IDS, filed 12/06/2001, 03/28/2003, and 10/22/2003, are acknowledged.

References # 3, 7, 8, and 10 on IDS filed 03/28/2003 have been lined through as they are duplicates of references listed on other IDS.

6. The use of the trademarks has been noted in this application (e.g. "FastTrack 2.0" mRNA isolation kit, on page 178, bottom paragraph). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

In addition, Applicant is requested to review the application for embedded hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01 and 608.01(p).

7. Claim 264 is objected to under 37 CFR 1.75 as being a duplicate of claim 263. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 259 – 296, 298, 301 and 368 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 259 and 291, and dependent claims thereof, are ambiguous in that it is unclear whether the phrase "expressed on a cell or bound to a cell membrane" is intended to refer to "human B7-1" or "the isolated or recombinant polypeptide."

(B) Claim 290 recites the limitation " the polypeptide of claim 288, wherein the modified amino acid..." There is insufficient antecedent basis for this limitation in claim 288.

It appears that claim 290 was intended to depend on claim 289, and is treated as such for examination purposes in the instant office Action.

(C) Claim 291, and dependent claims thereof, are ambiguous in the recitation of "residues at positions 35 – 244," as it is unclear to which sequence these numbers refer.

(D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 261 – 264, 269 – 270, 273, 276 – 277, 284 – 285, 292, 296, and 299 – 301 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

(A) The following ranges of amino acid residues of SEQ ID NO:66, claimed in the claims listed above, represent a departure from the specification and the claims as originally filed, and applicant has not pointed out where the support comes from:

"35 – 244, 35 – 245, 245 – 268, 246 – 272, 269 – 303, 273 – 303, 35 – 303, 1 – 268, and 1 – 272."

The specification and the claims as originally field only support the ranges of e.g. amino acids 35 – 242 of B7-1, not of SEQ ID NO:66 (e.g. page 24 line 19).

(B) Claim 292 includes a recitation of "binding affinity ratio about greater than," which represents a departure from he specification and the claims as originally filed, and applicant has not pointed out where the support comes from.

(C) The specification as filed does not provide a written description nor direction for the instant claims encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.05-06 and 2173.05(i).

12. Claims 259 – 262, 265 – 278, 280 – 290, and 298 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a sufficient enabling description of the claimed invention.

The limitations of "extracellular domain," "signal peptide," transmembrane domain," "mature domain," and "cytoplasmic domain" as they refer to the sequences having a certain percent identity to SEQ ID NO:66, were not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Although the definitions of these domains as they refer to SEQ ID NO:66 are set forth in the instant specification (e.g. in Fig. 2), there is insufficient guidance in the specification with regard to the boundaries of the respective functional domains in homologous polypeptides. Without sufficient guidance, the specific sequences which would encompass the functional domains are unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

13. Claims 289 and 290 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that for examination purposes claim 290 is assumed to depend on claim 289 rather than claim 288 (see section 9(C) above).

The specification does not provide a sufficient enabling description of the claimed invention.

The instant claim language encompasses a polypeptide comprising modified amino acids. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al. (J Cell Biol., 1990, Vol. 111, pp. 2129-2138; in particular, pages 2132 - 2133) show that a conservative replacement of a single "lysine" reside at position 132 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol., 1988, Vol. 8, pp. 1247-1252; in particular, page 1250 and Table 1) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, Metzler et al. (Nature Structural Biol., 1997, Vol. 4, pp. 527-531; in particular, pages 728 – 729 and Table 2) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification discloses on page 17 and in claim 290 a number of possible chemical modifications of amino acids. However, the specification fails to teach what modifications of the disclosed sequences can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid modifications are possible in any given protein, the position within the protein's sequence where such amino acid modifications can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative modifications or no modifications. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al., Science, 1990, Vol. 247, pp. 1306-1310; in particular, page 1306, col. 2).

Thus the recitation of a range of possible amino acid modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not allow the skilled artisan to make and use the claimed polypeptides commensurate in scope with the instant claims without undue experimentation.

14. Claim 368 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

There is insufficient guidance and direction as to how to make and use a polypeptide which is specifically bound by a polyclonal antisera raised against the polypeptide of claim 259.

The genus encompasses polypeptides recognized by antibodies that can bind to polypeptides which themselves have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes.

However, the present specification fails to provide sufficient disclosure of such polypeptides that maintain the structural and functional properties of the polypeptide set forth in SEQ ID NO:66. The specification does not provide sufficient guidance as to which of the amino acids may be changed while structural or functional activity and specificity is retained. For example, Lederman et al. (Molecular Immunology, 1991, vol. 28, pp. 1171-1181) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Likewise, Coleman et al. (Research in Immunology, 1994, vol. 145, pp. 33-36) teach that single amino acid changes in an antigen can effectively abolish antibody antigen binding, and Abaza et al. (Journal of Protein Chemistry, 1992, vol. 11, pp. 433-444) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding.

Because of this lack of guidance, the extended experimentation that would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Burgess et al. (J Cell Biol., 1990, Vol. 111, pp. 2129-2138; in particular, pages 2132 - 2133), it would require an undue amount of experimentation for one of skill in the art to arrive at the other polypeptides encompassed by the claimed invention.

The scope of the claimed polypeptides which are specifically bound by a polyclonal antisera raised against the polypeptide of claim 259 is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of such polypeptides broadly encompassed by the claimed invention. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's or peptide's amino acid sequence, and, in turn, nucleic acid sequence, and still retain similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a limited number of proteins/nucleic acids and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed polypeptides in manner reasonably correlated with the scope of the claims broadly including a broad number of structural changes encompassed by 91% sequence identity. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the claimed polypeptide and still maintain biological activity or structural specificity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 259 – 262, 264 – 267, 271, 277, 281, 283 – 286, 288, 297 - 298, and 368 are rejected under **35 U.S.C. 102(b)** as being anticipated by Parsons et al. (Immunogenetics, 1999, vol. 49, pp. 231 – 234; see entire document).

It is noted that for the purposes of examination, it is assumed that the "extracellular domain" as referred to in claim 259 encompasses amino acids 35 – 242 of SEQ ID NO:66, as shown in Figure 2A.

Parsons et al. teach the sequence of cattle CD80 protein, which is 90% identical in sequence to amino acids 35 – 242 of SEQ ID NO:66. Thus, the teachings of Parsons et al. anticipate the claimed limitations of "at least about 91% (or 95%) sequence identity" to the extracellular domain of SEQ ID NO:66. The claimed functional

limitations of binding affinity or inducing T-cell proliferation would be inherent properties of the referenced polypeptide.

Claim 368 is included because a polypeptide taught by Parsons et al. sharing extensive stretches of amino acid sequence identity with the polypeptide of SEQ ID NO:66, would necessarily be specifically bound by a polyclonal antisera raised against a polypeptide of claim 259.

The reference teaching thus anticipates the claimed invention.

17. Conclusion: No Claim is allowed.

18. It is noted that in the event Applicant amends the claims to include multiple specific sequences, e.g. such as SEQ ID NOS:48 – 68, an election of species will be required. Further, the Examiner would request Applicant's cooperation in providing a "consensus" sequence and pointing out the most divergent variants of the claimed sequences.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
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September 17, 2004

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